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GB A 2111386 GB 1546448 GB 1405088
GB A 2065145

(58) Field of search
A5B

(54) Bromocriptine compositions

(57) Oral controlled release formulations comprise bromocriptine, a hydrophilic swelling substance and an inert fatty material.

EXHIBIT 313

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FIG. 1

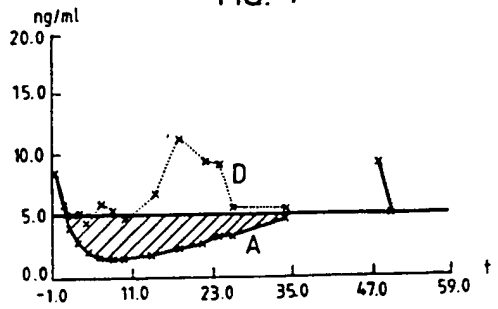


FIG. 2

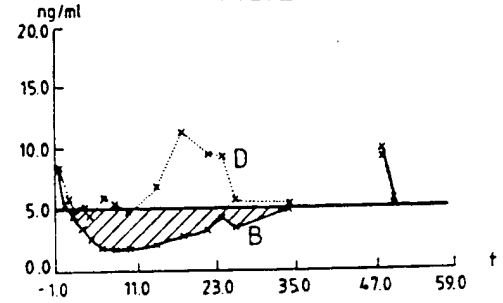


FIG. 3

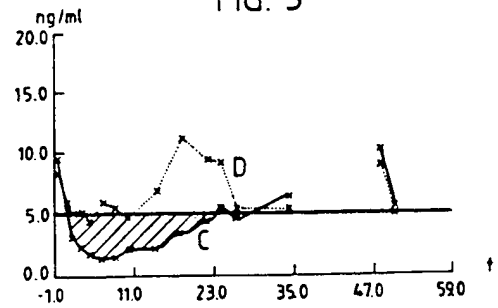
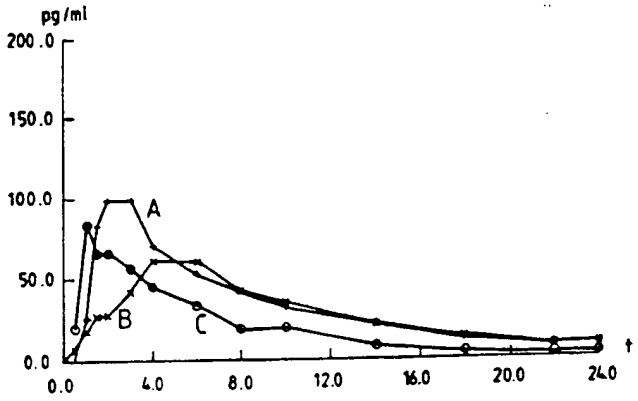


FIG. 4


pg/ml
200.0
150.0
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8.0
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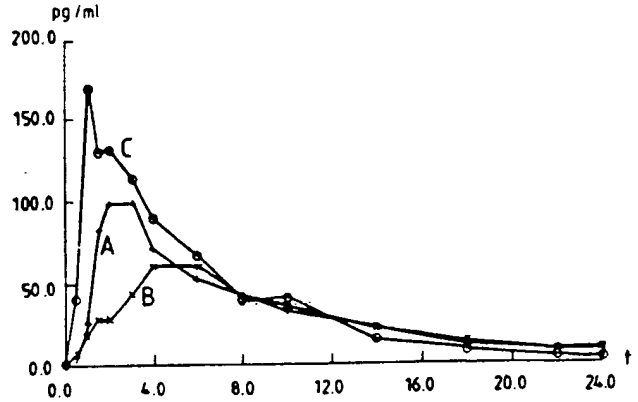
t

FIG. 5


pg/ml
200.0
150.0
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A
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t

SPECIFICATION

Bromocriptine compositions

This invention relates to pharmaceutical compositions, containing bromocriptine.

Bromocriptine is the generic name for the compound 2-bromo-12'-hydroxy-2'-(1-methylethyl)-5'α-(2-methylpropyl)ergotamin-3',6-tri-one and is listed in the Merck Index, 1976, Appendix A 2.

Bromocriptine is a well-known dopamine agonist used in the treatment of e.g. hyperprolactinemia, acromegaly and Parkinson's disease. It is usually administered in the form of the mesylate in daily dosages of e.g. 5–7.5 mg, 10–60 mg and 20–80 mg respectively. Its pharmacological and clinical properties have been recently extensively reviewed in M.O. Thorner et al.: Bromocriptine A clinical and pharmacological review, Raven Press, New York 1980. However the pharmacokinetic profile was not been established conclusively. From extensive pharmacokinetic studies we have found that bromocriptine is rapidly absorbed and rapidly eliminated from plasma after oral administration (t 1/2 = 3 to 5 hours). Although its duration of action appears to extend well beyond t 1/2 in some applications (e.g hypoprolactinaemia effect), we have found that it is generally necessary to administer the daily doses in 2 to 4 small doses to achieve a lasting therapy and to decrease potential unwanted side effects, which are thought to be related to the rapid absorption of the drug. Some of these side effects are due to dopaminergic activity of the compound acting on dopaminergic receptors in the gastro-intestinal tract, e.g. nausea and emesis.

There exists thus a need for a controlled release formulation of bromocriptine which provides a prolonged action of bromocriptine to reduce the number of times bromocriptine has to be administered each day and to reduce certain adverse reactions.

The present invention provides a controlled release formulation for oral administration comprising

bromocriptine

a pharmaceutically acceptable hydrophilic swelling substance and a pharmaceutically acceptable inert fatty material.

The preferred amounts of bromocriptine in the unit dosage form are from 2 to 20 mg, especially 5 and 10 mg. The bromocriptine may be in free base form or in the form of a pharmaceutically acceptable acid addition salt. Preferably the bromocriptine is in mesylate salt form. Reference herein to bromocriptine is intended both the free base form and such salts forms.

Hydrophilic swelling substances that can be used include one or more natural, partially or totally synthetic anionic or, preferably, nonionic hydrophilic gums, modified cellulosic substances or proteinaceous substances such as, for example, acacia, gum tragacanth, locust bean gum, guar gum, karaya gum, agar, pectin, carrageen, soluble and insoluble alginates, methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, sodiumcarboxymethylcellulose, carboxypolymethylene, gelatin.

Preferred are cellulose hydrocolloids which include methyl cellulose, hydroxypropylcellulose and especially hydroxypropylmethylcellulose and sodium carboxymethylcellulose. Preferably the weight ratio of bromocriptine to the hydrophilic swelling substance is from 1:10 to 1:35, especially from 1:16 to 1:25.

The weight ratios refer to the amount of active substance bromocriptine, not the total weight of any salt.

Usable pharmaceutically acceptable inert fatty materials include beeswax; fatty acids; long chain fatty alcohols such as, for example, cetyl alcohol, myristyl alcohol, stearyl alcohol, glycerides such as glyceryl esters of fatty acids or hydrogenated aliphatic acids such as, for example, glyceryl monostearate, glyceryl distearate, glyceryl esters of hydrogenated castor oil and the like; oils such as mineral oil and the like. Fatty materials are preferably such with melting points between 30 and 90°C.

Most preferred fatty materials have a melting point from 45°C to 65°C and include glycerides such as glyceryl palmitates and stearates and fatty acids such as hydrogenated castor oil and fatty acid esters such as cetyl palmitate. Preferably the weight ratio of bromocriptine to the fatty material is from 1:1 to 1:10, especially from 1:6 to 1:10.

It is also convenient to incorporate in the formulation other soluble or insoluble pharmaceutical excipients such as calcium sulfate, calcium phosphate, lactose and colloidal silica. The weight ratio of bromocriptine to these other excipients is conveniently from 1:5 to 1:40, e.g. 1:15 to 1:40.

The formulation may be produced in conventional manner by mixing the ingredients together, if desired melting the fatty material. The resultant mixture is in powder form. The powder can be

fact that bromocriptine is sensitive to many chemical reagents. Moreover, the formulations have a satisfactory pharmacodynamic and pharmacokinetic profile.

The resultant retarded formulations in general have comparable bio-availability in standard clinical trials to conventional non-retarded formulations containing the same amount of bromocriptine. The formulations of the invention, even if administered once a day, can still produce a therapeutic effect for at least 24 hours and even as much as 35 hours. The formulation may thus be administered only once a day in the known indications of bromocriptine at approximately the same daily doses as employed in the conventional non-retarded forms.

Preferred formulations such, which shown in in vitro release experiments a release rate of bromocriptine of less than 50% in 2,5 hours, preferably a release rate of less than 65% in 8 hours, as measured in 0,1 n HCl solution. Most preferably, the formulation will release at least 80% of the active ingredient within 24 hours.

In the following examples all temperatures are in degrees Centigrade and are uncorrected.

Further information on the properties etc. of the pharmaceutical excipients named hereinafter may be obtained from the manufacturer, listed hereinafter, manufacturer's brochures or other sources, especially H.P. Fiedler Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete, 2nd Edition 1981, Edito Cantor Aulendorf, W. Germany.

Silica is e.g. brand Aerosil 200 available from Deutsche-Gold und Siberscheidanstalt, Frankfurt, W. Germany.

Glycerol ditripalmitostearate is e.g. brand Precirol Ato 5 available from ETS Gattefosse 929100 Voulogne-Brillancourt, France.

Hydroxypropylmethylcellulose 15000 cps and 4000 cps are e.g. brands Methocel K15M and Methocel E4M available from Dow Chemical Company, Michigan 48640 USA.

Cetyl palmitate is e.g. brand Cutina CP available from Henkel 4000, Düsseldorf, W.Germany.

EXAMPLE 1: Composition of each capsule

	Ingredient	mg
1)	Bromocriptine mesylate	5.735 *)
2)	Lactose (200 mesh)	124.265
3)	Silica	10
4)	Glycerol ditripalmitostearate	40
5)	Hydroxypropylmethylcellulose 4000 cps	110
		290
	Capsule (Hard gelatine)	78

*)equivalent to 5 mg bromocriptine base

Preparation (Charge of 6000 capsules)

Ingredients 1), 2) and 3) are sieved and mixed. Ingredient 4) is melted by heating to 56°C (m.p. 54°C) and is added to the mixture which is heated to 55°C. The mass is stirred for 2 minutes or until it is a homogenous mixture and cooled overnight. The crushed mass is broken up and sieved (through 250 micron openings). Ingredient 5) is sieved (through 360 micron openings) and mixed in over 10 minutes. The mixture is then encapsulated.

In vitro release

Gastric juice 0.1 n HCl (pH 1.2)

Time (hours)	Release of bromocriptine
1	7%
2	13%
4	28%
6	42%
24	100%

EXAMPLE 2: Composition of each capsule

	Ingredient	mg
1)	Bromocriptine mesylate	5.735 *)
2)	Calcium sulfate . $2H_2O$	124.265
3)	Cetypalmitate	20.0
4)	Hydroxypropylmethylcellulose (15000 cps)	120.0
		270.0
	Capsule (hard gelatine)	78.0

*)equivalent to 5 mg bromocriptine base

Preparation

Analogous to Example 1, with the difference, that now igredients 1) and 2) are mixed, followed by addition of ingredient 3) in molten form, after which the mixture is cooled and ingredient 4) is added.

EXAMPLE 3: Composition of each capsule

	Ingredient	
1)	Bromocriptine mesylate	11.47
2)	Maleic acid	4.00
3)	Lactose	78.53
4)	Silica	10.00
5)	Cetyl palmitate	40.00
6)	Hydroxypropylmethylcellulose 15.000 cps	130.00
		274.00
	Capsule (hard gelatine)	81.00

3*)corresponding to 10 mg bromocriptine base

Preparation

Analogous to Example 1, with the different that now ingredients 1), 2), 3) and 4) are mixed, followed by addition of ingredient 5) in molten form, after which the mixture is cooled and ingredient 6) is added.

Comparative clinical tests

Objectives: To study in healthy volunteers the tolerability, bioavailability and the prolactine suppression effects of two oral controlled release capsules A and B according to the invention in comparison to a conventional capsule C and a placebo capsule D.

A. Composition according to the invention

	Ingredient	mg
1.	Bromocriptine in mesylate form	5.735 *)
2.	Lactose	184.265
3.	Glycerol-ditripalmito stearate	20.000
4.	Hydroxypropylmethylcellulose (400 cps)	60.000

*)corresponding to 5 mg bromocriptine

The fatty acid component A3. was added in molten form to a mixture of components A1. and A2. and mixed therewith after which the mixture was cooled to room temperature and component A4. was mixed with the mixture of A1., A2. and A3.

B. Composition according to the invention

Ingredient	mg
1. Bromocriptine in mesylate form	5.735
2. Lactose	124.265
3. Silica	10.000
4. Glycerol-ditripalmito stearate	40.000
5. Hydroxypropylmethylcellulose (4000 cps)	110.000

The mixture was prepared analogous to the mixture under A, with the exception that instead of mixing A1. and A2., B1., B2. and B3. were mixed.

[redacted]

Ingredient	mg
1. Bromocriptine in mesylate form	2.87 *)
2. Maleic acid, milled	2.00
3. Lactose	170.63
4. Cornstarch	120.00
5. Silica	1.50
6. Magnesiumstearate	3.00

*)corresponding to 2,5 mg bromocriptine

The ingredients 1 to 6 were mixed together

D) Conventional placebo composition

Ingredient	mg
1. Lactose	190.00
2. Glycerol ditripalmito stearate	20.00
3. Hydroxypropylmethylcellulose (4000 cps)	60.00

The fatty component D2 was added in molten form to component D1 and mixed therewith, after which the mixture was cooled to room temperature and mixed with component D3.

Instead of 5 mg bromocriptine, as present in capsule A and B, the non-retarded capsule C contained only 2.5 mg bromocriptine to avoid a too strong influence on the healthy volunteers by expected side effects.

In a randomized double-blind design 8 healthy male volunteers received at 8.00 h in the morning either one capsule A, B, C or D in such a manner that each volunteer received the 4 different capsule types, divided over 4 administration days, separated by an interval of a week.

Prolactin inhibition

Blood samples were obtained from the 8 volunteers by an indwelling cannula, in certain time intervals from 8.00 h, the time the capsule was received, till 10.00 h on the third day (totally 50 hours); with a longer interruption from 18.00 till 8.00 h in the second night. The prolactin levels were determined by a specific radioimmunoassay.

The prolactin concentrations, measured after the administration of capsules A, B and C were plotted graphically as corresponding mean curves A (Fig. 1), B (Fig. 2) and C (Fig. 3).

The prolactin concentrations, determined after the administration of capsule D, were depicted as curve D in Fig. 1, 2 and 3, which was compared with curves A, B and C (in nanograms/ml, time t in hours).

The prolactin curve D represents the normal prolactin concentration of healthy volunteers during night and day.

In the evening, the concentration rises, during sleep the maximum is reached and in the first wakening hours the concentration falls to a day-time "basal level" which is maintained to about 20.000 h. From curves A and B a prolactin secretion inhibition is observed 1 hour after taking the corresponding capsules A and B and lasting 35 hours.

Capsule C produces a prolactin inhibition in healthy volunteers, 1 hour after taking a capsule C and lasting only 24 hours.

4 (in picograms/ml, time t in hours).

The concentrations of curve C in Fig. 4, caused by the 2.5 mg bromocriptine containing capsule C were doubled and plotted in Fig. 5 as a curve C adapted to a double portion of capsule C, together with curves A and B, so that bromocriptine levels of equal dosages of bromocriptine (5 mg) can be compared.

From Fig. 5 it is seen that the rate at which drug concentrations initially rise (i.e. absorption phase) is slightly reduced for form A and markedly reduced for form B as compared with twice form C.

It also appears from these mean curves, that bioavailabilities (AUC*) of capsules A and B are somewhat lower than of two capsules C.

*Area under curve

Based on the individual subjects data, the reduction in bioavailability was an average of 12% for form A and 25% for form B.

Tolerability

The side effects experienced by each volunteer were recorded as to type, duration and intensity (strong, moderate and weak). Overall the following side effects were noted:—

1) orthostatic hypotonia
2) dizziness
3) vomiting
4) nausea
5) nasal congestion
6) headache
7) dry mouth
8) head pressure
9) drowsiness
10) tiredness
11) weakness
12) sweating
13) heat sensation
14) abdominal cramps
15) palor

side effects 1) to 6) are well known for dopamine agonist drugs like Bromocriptine and were used to assess the relative tolerability of the formulations in the table below:

	number of drug related side effects			
Intensity	A 5 mg drug	B 5 mg drug	C 2.5 mg drug	D placebo
strong	10	5	1	1
moderate	16	9	1	0
weak	12	5	11	3
total	38	19	13	4

Capsule A produces significantly more drug related side effects than all other forms.

Capsule B produced fewer drug related side effects than A, and the total number was not statistically different from the 2.5 mg conventional form C.

Capsule C produced significantly more drug related side effects than placebo D.

On the basis of tolerability, Capsule B is to be preferred over capsule A.

In in vitro experiments (USP XXI, page 1243–1244, Apparatus 1, 1000 ml 0.1 n HCl, 100 rotations per min.) the following release results were obtained with capsules A, B and C:—

Release time in hours	Release of bromocriptine (in percents of weights)		
	Capsule A	Capsule B	Capsule C
0,5	13	4	99
1	23	8	100
2	42	15	
4	66	28	
6	81	39	
8	89	48	
10	94	57	
14	98	68	
24	100	86	

From the viewpoint of pharmacokinetics capsules A and B are preferred and capsule B is especially preferred.

Summary:
—A daily dosage of two capsules of C, if administered simultaneously, would not be tolerated in clinical practice as reported before.
—Both capsules A and B, if administered once a day surprisingly cause a satisfactory therapeutically effective bromocriptine concentration for 24 hours and a prolactin suppression for 35 hours in the blood, notwithstanding a slightly decreased bioavailability in comparison with two capsules C. Capsule B is preferably used, since it causes less side effects and its controlled absorption is better.

CLAIMS

1. A controlled release formulation for oral administration comprising
—bromocriptine
—a pharmaceutically acceptable hydrophilic swelling substance
—a pharmaceutically acceptable inert fatty material.

2. A formulation according to claim 1 containing 2 to 20 mg of bromocriptine per unit dosage form.

3. A formulation according to claim 2 containing 5 mg bromocriptine.

4. A formulation according to claim 2 containing 10 mg bromocriptine.

5. A formulation according to any one of the preceding claims wherein the swelling substance is a cellulose hydrocolloid.

6. A formulation according to any one of the preceding claims wherein the swelling substance is hydroxypropylmethylcellulose.

7. A formulation according to any one of the preceding claims wherein the weight ratio of bromocriptine to the swelling substance is from 1:10 to 1:35.

8. A formulation according to any one of the preceding claims wherein the weight ratio of the swelling substance to bromocriptine is from 1:16 to 1:25.

9. A formulation according to any one of the preceding claims wherein the fatty acid material is a hydrophobic material with a melting point between 30 and 90°C.

10. A formulation according to any one of the preceding claims wherein the fatty material has a melting point from 45 to 65°C.

11. A formulation according to any one of the preceding claims wherein the fatty material is a glyceride.

12. A formulation according to claim 11 wherein the glyceride is glycerol ditripalmitostearate.

13. A formulation according to any one of the preceding claims wherein the weight ratio of bromocriptine to the fatty material is from 1:1 to 1:10.

14. A formulation according to claim 13 wherein the weight ratio is from 1:6 to 1:10.

15. A formulation according to any one of the preceding claims containing hydroxypropylmethylcellulose as a swelling agent and glycerol ditripalmitostearate as a fatty material.

16. A formulation according to claim 15, containing bromocriptine, hydroxypropylmethylcellulose and glycerol ditripalmitostearate in a weight ratio of about 1:22:8 or 1:12:4.

17. A method for the preparation of a controlled release formulation for oral administration, which comprises mixing bromocriptine, hydrophilic swelling substance and a fattay material.
... hyperprolactinemia, acromegaly, or Parkinson's

Release time in hours	Release of bromocriptine (in percents of weights)		
	Capsule A	Capsule B	Capsule C
0,5	13	4	99
1	23	8	100
2	42	15	
4	66	28	
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—a pharmaceutically acceptable inert fatty material.

2. A formulation according to claim 1 containing 2 to 20 mg of bromocriptine per unit dosage form.

3. A formulation according to claim 2 containing 5 mg bromocriptine.

4. A formulation according to claim 2 containing 10 mg bromocriptine.

5. A formulation according to any one of the preceding claims wherein the swelling substance is a cellulose hydrocolloid.

6. A formulation according to any one of the preceding claims wherein the swelling substance is hydroxypropylmethylcellulose.

7. A formulation according to any one of the preceding claims wherein the weight ratio of bromocriptine to the swelling substance is from 1:10 to 1:35.

8. A formulation according to any one of the preceding claims wherein the weight ratio of the swelling substance to bromocriptine is from 1:16 to 1:25.

9. A formulation according to any one of the preceding claims wherein the fatty acid material is a hydrophobic material with a melting point between 30 and 90°C.

10. A formulation according to any one of the preceding claims wherein the fatty material has a melting point from 45 to 65°C.

11. A formulation according to any one of the preceding claims wherein the fatty material is a glyceride.

12. A formulation according to claim 11 wherein the glyceride is glycerol ditripalmitostearate.

13. A formulation according to any one of the preceding claims wherein the weight ratio of bromocriptine to the fatty material is from 1:1 to 1:10.

14. A formulation according to claim 13 wherein the weight ratio is from 1:6 to 1:10.

15. A formulation according to any one of the preceding claims containing hydroxypropylmethylcellulose as a swelling agent and glycerol ditripalmitostearate as a fatty material.

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3. A formulation according to claim 2 containing 5 mg bromocriptine.

4. A formulation according to claim 2 containing 10 mg bromocriptine.

5. A formulation according to any one of the preceding claims wherein the swelling substance is a cellulose hydrocolloid.

6. A formulation according to any one of the preceding claims wherein the swelling substance is hydroxypropylmethylcellulose.

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10. A formulation according to any one of the preceding claims wherein the fatty material has a melting point from 45 to 65°C.

11. A formulation according to any one of the preceding claims wherein the fatty material is a glyceride.

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13. A formulation according to any one of the preceding claims wherein the weight ratio of bromocriptine to the fatty material is from 1:1 to 1:10.

14. A formulation according to claim 13 wherein the weight ratio is from 1:6 to 1:10.

15. A formulation according to any one of the preceding claims containing hydroxypropylmethylcellulose as a swelling agent and glycerol ditripalmitostearate as a fatty material.

16. A formulation according to claim 15, containing bromocriptine, hydroxypropylmethylcellulose and glycerol ditripalmitostearate in a weight ratio of about 1:22:8 or 1:12:4.

17. A method for the preparation of a controlled release formulation for oral administration, which comprises mixing bromocriptine, hydrophilic swelling substance and a fattay material. [illegible] hyperprolactinemia, acromegaly, or Parkinson's

or Parkinson's disease according to the method of claim 18 in unit dosage form, containing 2 to 20 mg of bromocriptine.

20. A formulation according to claim 1 substantially as hereinbefore described with reference to any one of the Examples.

21. A controlled release formulation of bromocriptine releasing less than 50 percent by weight of bromocriptine within 2.5 hours as measured in 0,1 n HCl in in vitro release experiments.

22. A controlled release formulation according to claim 21 releasing less than 65 percent by weight within 8 hours.

23. A controlled release formulation according to claims 21 or 22 releasing at least 80 percent by weight within 24 hours.

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